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SHORT ORIGINAL ARTICLE / *Gastrointestinal imaging*

Interest of contrast-enhanced sonography to identify focal nodular hyperplasia with sinusoidal dilatation

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Contrast-enhanced ultrasound;
Glutamine synthetase

Abstract
Background and aims: Focal nodular hyperplasia with major sinusoidal dilatation (FNH-sd) is a misleading entity, with some features resembling inflammatory hepatocellular adenoma (HCA). We aimed to assess the performance of contrast-enhanced ultrasound (CEUS) for the diagnosis of FNH-sd.
Methods: Four histologically proven FNH-sd nodules in four patients were investigated with both MRI and CEUS imaging. Sinusoidal dilatation was focally visible in all cases in histology.
Results: In MRI, in all the four cases, lesions were hypervascular in arterial phase, with high intensity in T2-weighted sequence imaging and persistent enhancement in the delayed gadolinium-enhanced phase. These MRI features were more indicative of HCA than FNH. On the other hand, CEUS showed a very specific centrifugal filling followed by a strong, homogeneous enhancement of the whole lesion.
Conclusion: CEUS seems to be an essential step for the diagnosis of non-typical FNH, such as FNH-sd. This small series highlights the interest of performing both CEUS and MRI for the diagnosis of atypical focal liver lesions, such as FNH-sd.

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Abbreviations

FNHa	focal nodular hyperplasia
HCA	hepatocellular adenoma
MRI	magnetic resonance imaging
FNH-sd	focal nodular hyperplasia with sinusoidal dilatation
TFNH	telangiectasic focal nodular hyperplasia
GS	glutamine synthetase
LFBAP	liver fatty acid-binding protein
CRP	C-reactive protein
SAA	serum amyloid A
HNF1 α	Hepatocyte nuclear factor-1 alpha
US	ultrasound
CEUS	contrast-enhanced ultrasound
AASLD	American Association for the Study of Liver Diseases
CK7	cytokeratins 7

Introduction

Majority of focal liver lesions are benign in non-cirrhotic liver. Focal nodular hyperplasia (FNH) is the second most common benign liver tumor after hemangioma [1]. The prevalence is estimated at 0.9% of the general population [2]. Although FNH may affect both sexes of all ages, it is more common in females (80%—95%) in their third or fourth decade of life [2]. FNH is often solitary but may be multiple in approximately 20% of cases. The pathogenesis of FNH is not well understood, but it is thought to be a non-specific response to locally increased blood flow. This hypothesis is strengthened by the fact that FNH can also be associated with vascular abnormalities as hepatic hemangiomas [3]. In 1995, the International Working Party classified FNH with other regenerative lesions, in contrast to adenoma (HCA), which is known as a neoplastic lesion [4].

FNH is usually asymptomatic, and most cases are discovered incidentally on abdominal imaging. Clinical symptoms due to mass effect are infrequent. These lesions must still be correctly diagnosed because surgical resection is limited to symptomatic FNH, while the others are left untreated.

FNH in its typical form is an easy diagnosis with cross-sectional contrast-enhanced imaging. Thus, the imaging features of FNH include homogenous lesions, significant enhancement on the arterial phase with a lack of washout during the portal venous and delayed phases, peripheral lobulation and the presence of a central scar. Based on these criteria, CT and/or MRI have a sensitivity of 70% and a specificity of 100% for the diagnosis of FNH.

However, in daily practice, there are still some difficulties concerning less typical forms, such as pre/incomplete FNH, absence of central scar, presence of steatosis and sinusoidal dilatation. The so-called ''telangiectasic FNH'' (TFNH) was shown to be, at the histological level, closer to the family of hepatocellular adenomas (HCA) than to FNH itself [5,6]. Subsequently, it was shown that most of the so-called TFNH were inflammatory HCA [7]. More recently, the distinction between FNH and other lesions, like inflammatory HCA, has been largely solved with the progresses of molecular biology and its application in immunohistochemistry. Indeed, glutamine synthetase (GS), markedly overexpressed in FNH in a particular ''map-like pattern'', was used as a useful immunohistological marker to differentiate FNH from HCA [8]. Moreover, FNH does not express markers of HCA subtypes: particularly C-reactive protein (CRP) and serum amyloid (SAA) are negative, whereas they are overexpressed in inflammatory HCA. In addition, liver fatty acid-binding protein (LFABP) is normally expressed in FNH contrary to its absence in hepatocyte nuclear factor-1 alpha (HNF1α) mutated adenoma [7—9].

In this short article, we report four cases of histologically confirmed FNH with sinusoidal dilatation (FNH-sd). MRI and contrast-enhanced ultrasound (CEUS) data were retrospectively analysed to determine specific semiological pattern of these particular FNH type.

Methods

This retrospective and monocentric study had the approval of our Research Ethics Board for chart review.

We identified four patients with FNH-sd from December 2008 to November 2011 in the database of our pathology department. Histological, medical (including blood liver tests) and radiological data were collected and analyzed.

Histological analysis

Percutaneous needle biopsies were performed under ultrasonographic guidance using a 16—18 Gauge needle, according to the recommendations of the American Association for the Study of Liver Diseases (AASLD). At least two cores of liver tissue were obtained per patient.

The biopsy specimens were processed and paraffin sections were stained with H&E, Masson's trichrome, Perls. Additional immunostaining was performed, such as cytokeratins (K) 7 and 19, as well as glutamine synthetase (GS), serum amyloid A (SAA), C-reactive protein (CRP) and β-catenin.

MRI

MRI was performed on a 1.5 T MRI system (Achieva, Phillips Medical System, Best, The Netherlands), in our radiology department. For all MRI examination, the following sequences were acquired and analysed: axial in-phase and out-of-phase chemical-shift GRE T1-weighted (T1 W) images (repetition time/echo time, 208/2.3 and 4.6 msec; flip angle, 80°; field of view, 430 mm; matrix, 292 × 178; number of sections, 30; section thickness, 5.4 mm; two signals acquired); a respiratory-triggered, fat-suppressed, T2-weighted (T2 W) fast spin-echo pulse sequence (repetition time/echo time, 1,287/70 msec; flip angle, 90°; field of view, 450 mm; matrix, 308 × 156; number of sections, 30; section thickness, 5 mm; one signal acquired); a T2 W fast spin-echo pulse sequence (repetition time/echo time, 531/60 msec; flip angle, 90°; field of view, 395 mm; matrix, 256 × 136; number of sections, 25; section thickness, 6 mm; one signal acquired); and fat-suppressed dynamic gadolinium-enhanced T1 W gradient echo sequences during the arterial phase, late arterial phase, portal venous phase, and delayed phase, with manual administration of gadolinium-based contrast medium (repetition time/echo time, 4/1.92 msec; flip angle, 10°; field of view, 430 mm;

matrix, 192 × 138; number of sections, 37; section thickness, 5 mm; one signal acquired). The contrast agent used in all cases was Multihance® (Gadobenatediméglubine, Bracco, Milan, Italy). Additional hepatobiliary phase images were obtained at least 60 min after injection in only one case.

US and CEUS

All contrast-enhanced ultrasound were also performed in the radiology department, in the same machine (Acuson Sequoia®, Siemens Medical System, Erlangen, Germany), by a radiologist with at least 5 years of experience in CEUS. Baseline gray-scale sonography was performed to identify each hepatic lesion, after which low mechanical-index (0.07—0.2) contrast-enhanced sonography was performed after a contrast agent bolus injection of 0.1—0.3 mL. Injections were repeated two times. The contrast agent (Sonovue®, Bracco, Milan, Italy) was injected through a peripheral venous line by one of the department nurses.

Imaging evaluation

All MRI and contrast-enhanced ultrasound data were reviewed by three abdominal radiologists (H.L., H.T., N.F.) and discussed until there was a consensus. The three radiologists were blinded to the histological diagnoses. Some features were searched both in MRI and in CEUS. Others, considered to be specific to each of the methods, were searched in only one of the methods.

For both MRI and CEUS, we have analyzed the number of lesions, its location (according to Couinaud's numbering system), maximum diameter, as well as morphologic aspects such as limits (clearly or poorly delimited), borders (regular or lobulated) and appearance (homogeneous or heterogeneous).

For MRI, the following criteria were analysed: homogeneous or heterogeneous appearance of the lesion on each sequence; presence of fat deposition within the lesion (absence, focal or diffuse distribution in the lesion); presence of haemorrhagic and/or necrotic components; signal intensity on T1 W and T2 W imaging, type of enhancement at the arterial phase (homogenous-heterogenous), signal intensity of the lesion at the portal and delayed phase and when possible at the very delayed phase, so-called ''hepatobiliary phase'', presence of central scar, and accumulation of gadolinium chelates within the central area on delayed contrast-enhanced T1-weighted sequences. For the surrounding liver parenchyma: morphological feature (dysmorphy), and steatosis (homogenous/heterogenous), were collected.

For CEUS, the readers were asked to search and describe the behavior of the lesion during arterial, venous and late-venous phases (hyper-, iso-or hypovascular), the pattern of enhancement (centrifugal, centripetal or mixed), the presence of peripheral linear vascularities, a transient unenhanced zone and of a rim of persistent enhancement in the late venous phase. Central stellate arteries were defined by the presence of enhancing central arteries with a spoked-wheel or star like morphology. A central scar was defined as a central stellate hypoechoic linear or plicated area without contrast enhancement in the portal venous phase.

Results

Pathological results

Indications of liver biopsies were neoplastic context for one patient (case 1) and atypical aspect on MRI in all patients.

In histology, all the cases corresponded to a benign proliferation of hepatocytes without any cytological atypia; fibrous bands containing thick arteries were focally visible, with a few inflammatory cells associated. In one case, the ductular reaction was obvious; in two it was mild, underlined by K7 immunostaining. In all cases, sinusoidal dilatation was focally visible separating thin strands of hepatocytes.

In addition, GS immunostaining showed large positive hepatocytes areas (Fig. 1), often centered by veins, far from fibrous bands; there was no aberrant staining of β-catenin; SAA and CRP immunostainings were negative.

Clinical findings

The four patients included in the study were female and were from 32 to 46 years old with a mean age of 39 (± 7 years). Two of them (cases 2, 4) had no specific medical history. The lesions were discovered incidentally on ultrasound examinations performed for assessment of pelvic pain. The two remaining patients (cases 1 and 3) had a specific clinical setting: one patient (case 3) was followed for acquired immunodeficiency associated with HIV and her liver lesion was discovered during a CT scan performed to explore a chronic cough; the other one (case one1) was followed for melanoma. In these two cases, the lesions were, on CT images, hypodense, not well defined and non-specific. The contrast enhancement of lesions on CT scan was not studied. Transaminases were elevated (3 times the normal rate) in one patient (case 1).

MRI findings

The morphological characteristics of the nodules in MRI were a mean size of 23 mm (14 to 43 mm), hyperintensity on T2WI and hypointensity on T1. All lesions were homogeneous both on T1 and T2-weighted sequences and no signal dropout on chemical-shift sequences was found. No central scar was found. The lesions were located in segment VI (3 out of 4 lesions) and in segment V (1 out of 4). Hemorrhagic, necrotic, or fat components within the lesions were not identified in our cases. No liver dysmorphia was found. Steatosis in the healthy parts of the liver was observed in only one case (case 3). All lesions showed a strong arterial enhancement and had a persistent enhancement in the delayed phase. No wash out was found in any lesion. In the hepatobiliary phase images, obtained in only one patient, the nodule was hypointense to the surrounding liver parenchyma (Figs. 2 and 3).

US and CEUS findings

In non-enhanced B-mode ultrasound, the echogenicity was highly variable: mixed (1 nodule), isoechogenic (1 nodule), hyperechogenic (1 nodule) and hypoechogenic (1 nodule). A hyperechogenic ring was visualized in one lesion and a hypoechogenic ring in another one. During color and spectral

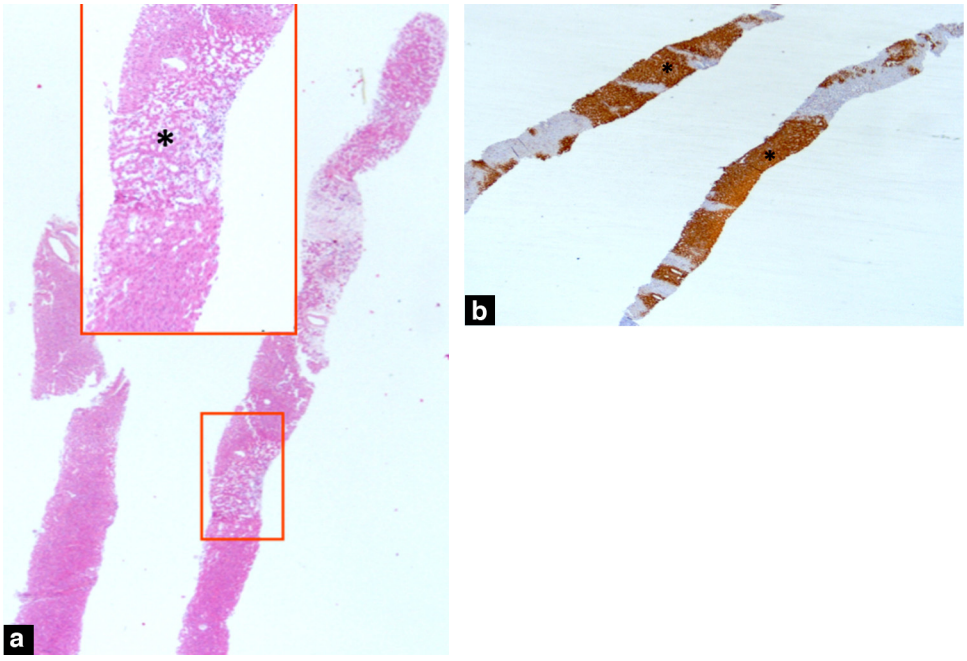

Figure 1. Biopsy of a liver lesion. In histology, presence of a proliferation of benign hepatocytes with (a) sinusoidal dilatation separating thin strands of hepatocytes (asterisk). GS immunostaining showed (b) large positive hepatocytes areas, often centered by veins, far from fibrous bands (asterisk). Case 1.

Doppler analysis, a central arterial pedicle with low resistance index was visualized in only one lesion.

After the injection of contrast, all the lesions showed hypervascularity in the arterial phase. We observed centrifugal filling in all cases, as well as the presence of stellate arteries and ''spoke wheel'' signs (100%). All lesions showed sustained portal venous phase enhancement for delayed phase (5 minutes) (Figs. 4 and 5).

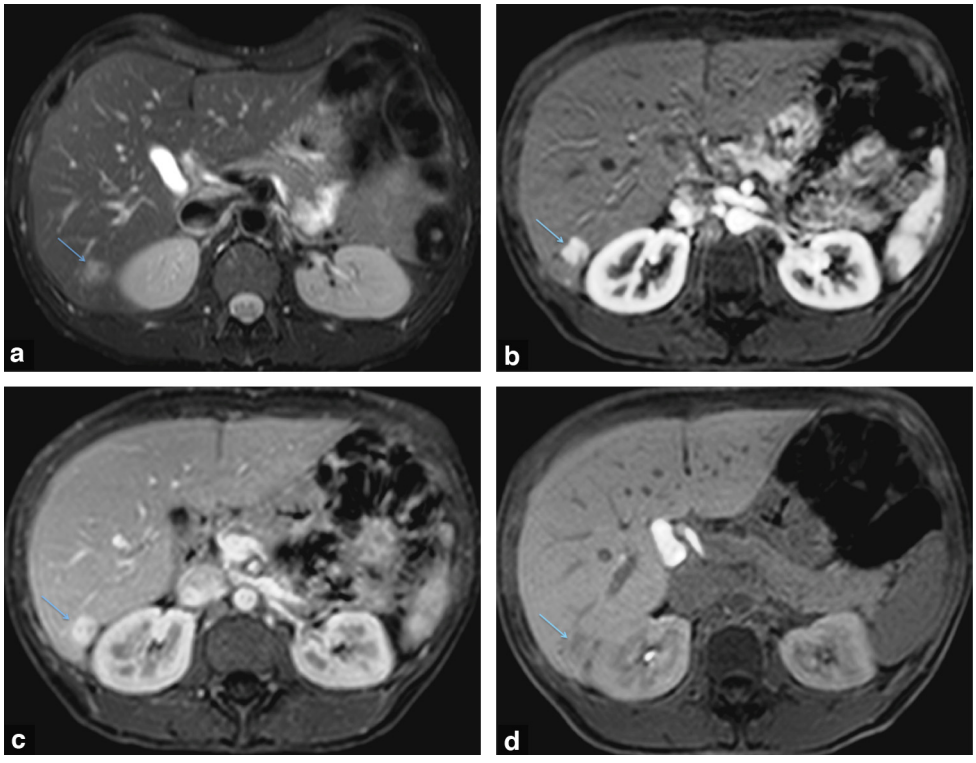

Figure 2. MRI. Segment 6 lesion with (a) an intense hypersignal on T2 W fast spin-echo pulse sequence, (b) strong arterial enhancement after gadolinium administration and (c) persistent enhancement at delayed phase (5mn) (arrows). In the hepatobiliary phase images (1H after injection) (d), the nodule was hypointense (arrow). Case 1.

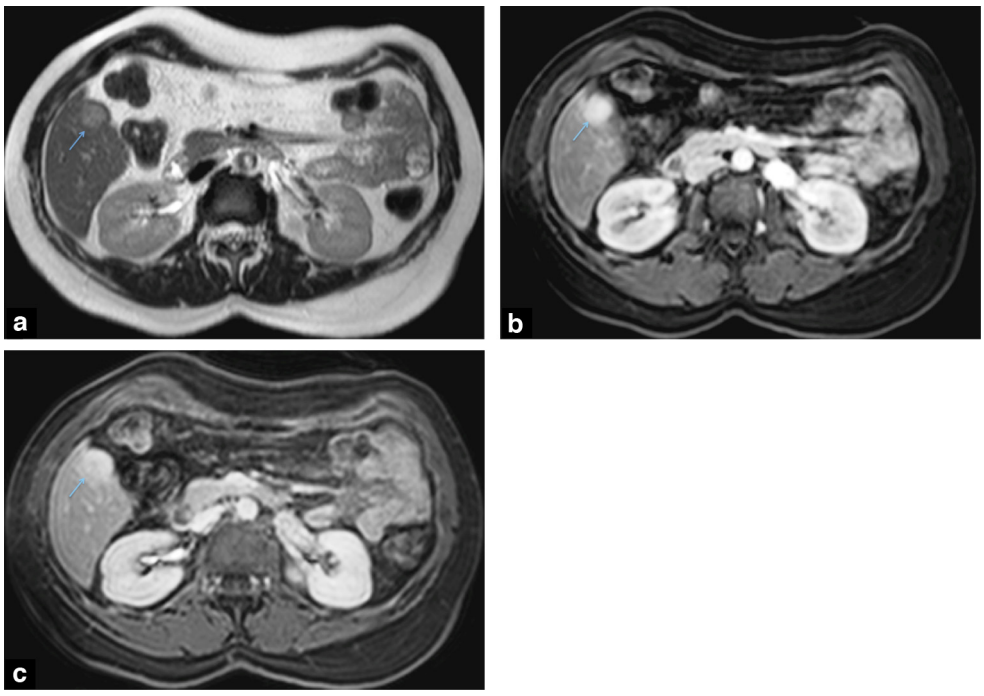

Figure 3. MRI. Segment 5 lesion with (a) an intense hypersignal on T2 W fast spin-echo pulse sequence, (b) strong arterial enhancement after gadolinium administration and (c) persistent enhancement at delayed phase (10 mn) (arrows). Case 2.

Discussion

It is of major clinical importance to differentiate FNH from HCA. Once the diagnosis of FNH is established, neither treatment nor follow-up are necessary (''do not touch lesion''). On the opposite, HCA requires follow-up if smaller and may indicate surgery if its size exceeds 5 cm, in order to avoid the risk of bleeding and malignant transformation. Unfortunately, the differential diagnosis between FNH and HCA by imaging techniques is far from easy in 10—20% of cases.

Among the difficulties to identify FNH, there could be the presence of sinusoidal dilatation. Sinusoidal dilatation

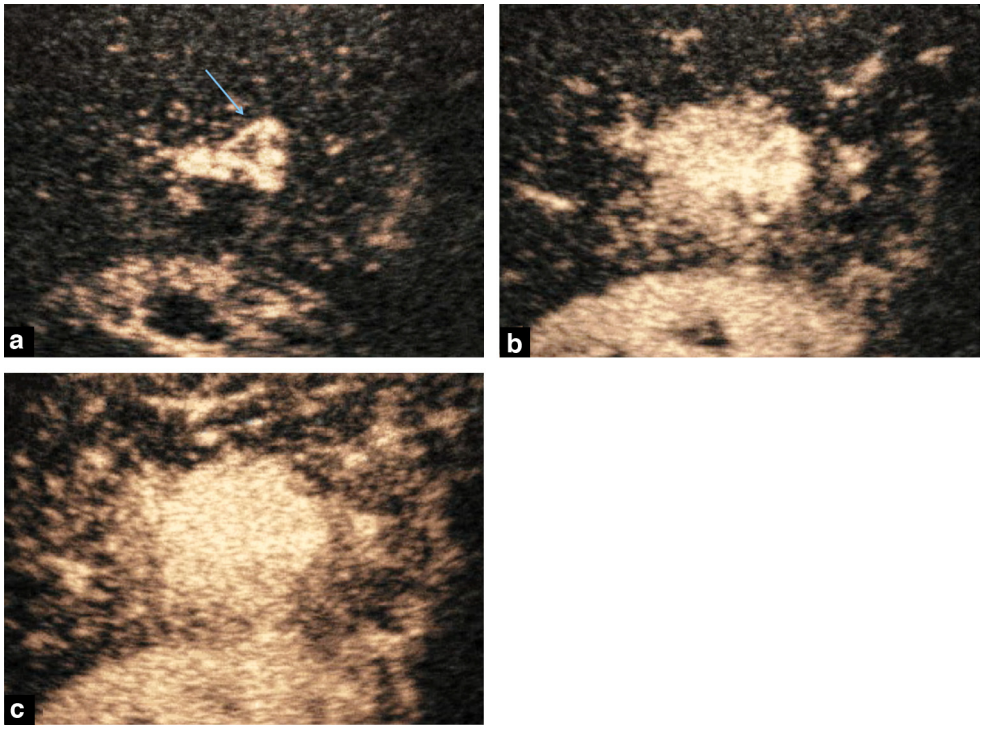

Figure 4. CEUS. The lesion shows (a) hypervascularity in the arterial phase with centrifugal filling and spoke wheel sign (arrow), following by (b, c) homogeneous enhancement of mass. Case 1.

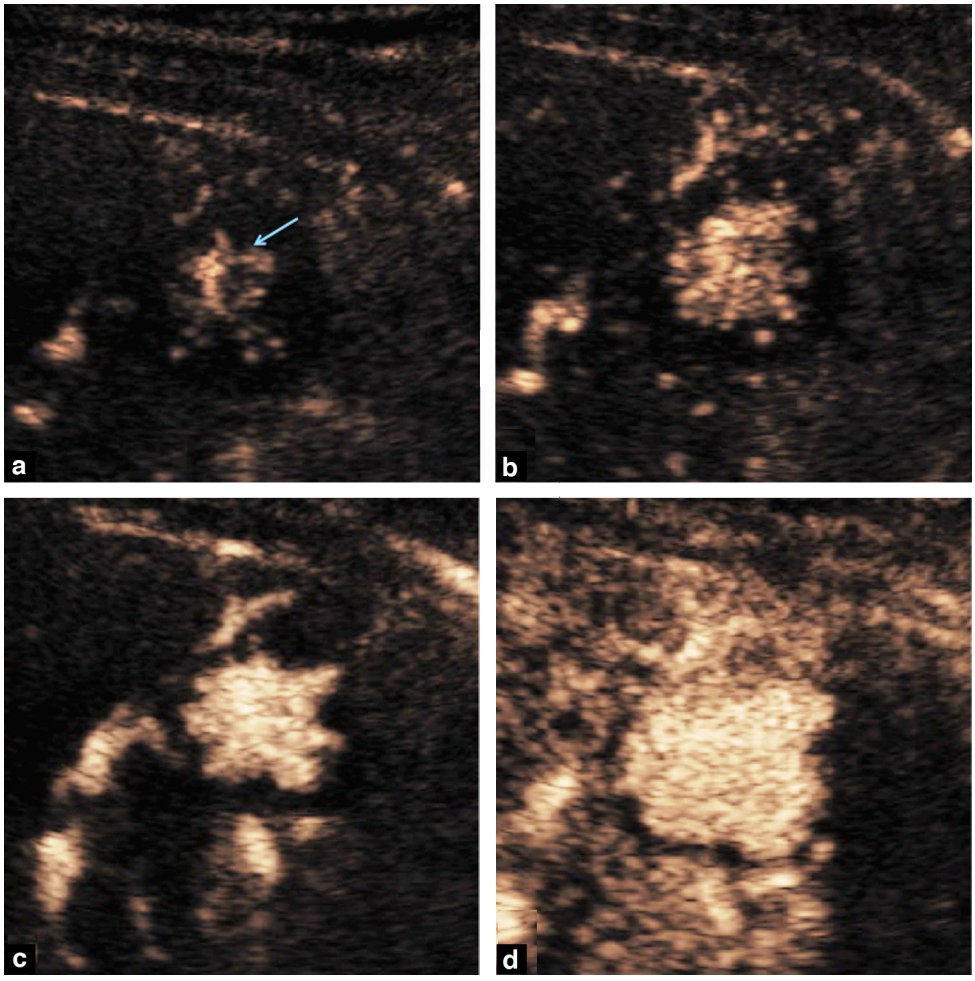

Figure 5. CEUS. The lesion (arrow), shows (a, b, c) hypervascularity in the arterial phase with centrifugal filling following by (d) homogeneous enhancement of mass. Case 2.

is one of the major histopathological criteria, in addition to inflammation, to identify inflammatory HCA. To what extent the entity TFNH, described in 1989 by Wanless [10] that does not belong to inflammatory HCA, exists and is similar to the term FNH with sinusoidal dilatation is unknown. Fortunately, nowadays the distinction between FNH and HCA has been largely solved with the progress made in the field of molecular biology and its applications in immunohistochemistry. Indeed, FNH expresses a very characteristic GS immunostaining [7] and does not express markers of HCA subtypes [9], especially CRP and SAA are negative, whereas they are overexpressed in inflammatory HCA and there is no aberrant β-catenin positive nuclei, contrary to β-catenin activated HCA. In addition, liver fatty acid-binding protein (LFABP) is normally expressed contrary to lack in HNF1α mutated adenoma. These differences apply to surgical specimen as well as core-biopsies [11].

Now, it is clear that FNH-sd does exist, and an observation of this particular type of FNH was already made previously [12]. Despite this misleading feature, the diagnosis can be made with appropriate imaging technique.

The important finding is that CEUS is an essential step to correctly identify FNH-sd. This is due most probably to the greater temporal resolution of CEUS than MRI, which shows centrifugal fillings, very specific of FNH.

It is often difficult to distinguish FNH-sd from inflammatory HCA in MRI. The presentation of the lesions is often almost identical and very atypical for FNH, since there is absence of central scar, hyperintensity on T2WI signal, hypointensity on TIWI and persistent enhancement at the delayed phase without any wash out. We think that these abnormalities of signal could be explained by the sinusoidal dilatation, a common feature in these two entities. Other signs may be helpful to distinguish these entities in MRI. Thus, the classic ''Atoll sign'', characterized by a hyperintense signal band in the periphery of the lesion (like an atoll) and isointensity of the center of the lesion with respect to the surrounding liver (like the surrounding sea) on T2-weighted images, is very specific of inflammatory HCA Unfortunately, this sign is inconstant (present in only 43% of inflammatory HCA in a previous study [13]).

On the opposite, on CEUS the lesions were hypervascular with radial vascular architecture, a feature characteristic of FNH lesions, suggesting that the kinetics of enhancement was more important than the morphological features.

However, in our study, the size of the lesions was small or intermidate and CEUS could be limited to appreciate the centrifugal filling and the stellate arteries, for bigger lesions.

In these cases, the use of liver-specific MRI contrast agents, such as Multihance® (Gadobenatedimeglubine, Bracco, Milan, Italy) or Primovist® (Gadoxetic acid, Bayer Healthcare, Germany), may help to differenciate these two entities by showing the biliary excretion product in FNH according to Grazioli et al. [14]. Indeed, FHNs always show bile ductular proliferation, whereas HCAs do not. In our series, only one patient was evaluated for hepatobiliary enhancement patterns and categorized as hypointense. Zech et al. reported that no enhancement occurred during the hepatobiliary phase in 10—12% of FNH [15]. In our case, we thought that sinusoidal dilatation could be the cause of the non-enhancement due to the rare (but present) ductules in this type of lesion, but it is difficult to affirm.

Conclusion

In this small series, we have shown four cases of FNH-sd in which the diagnosis was equivocal on MRI and was strongly suggested on CEUS. It is now clear that FNH-sd does exist and despite its misleading features, the diagnosis can be made with appropriate imaging techniques. CEUS is an essential step to correctly identify FNH-sd, which is most probably related to its greater temporal resolution when compared to MRI, leading to a better identification of centrifugal fillings and, therefore, the diagnosis of FNH. Thus, this small series highlights the interest of performing both CEUS and MRI for the diagnosis of atypical focal liver lesions, such as FNH-sd.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgments

The work presented here was carried out in collaboration between all authors. NF and HT defined the research theme. HT, NA and NF designed methods and analyzed the data, interpreted the results and wrote the paper. PBS and CB reviewed all histologicaldata. CB, PBS and HT discussed analyses, interpretation, and presentation.

We are indebted to our patients for allowing us to report their clinical courses.

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